AMENDMENTS TO THE CLAIMS

LISTING OF CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A method to determine a nucleotide sequence of a target nucleic acid, comprising

a) contacting the target nucleic acid, or a fragment thereof, with a population of capture oligonucleotide probes bound to a substrate at a series of spot locations, to form probe-target duplex nucleic acids comprising single-stranded overhangs;

b) contacting the probe-target duplex nucleic acids with a population of Raman-active oligonucleotide probes to allow binding of the Raman probes to the single-stranded overhangs, wherein each Raman-active oligonucleotide probe generates a distinct Raman signature, wherein at least one of the Raman-active oligonucleotide probes comprises a positively charged Raman signal enhancer, the positively charged Raman signal enhancer maintaining its positive charge after binding with the probe-target complex;

c) detecting Raman-active oligonucleotide probes that bind the template nucleic acid using Raman spectroscopy; and

d) identifying the location of the spot for each of the captured Raman-active oligonucleotide probes, thereby determining a nucleotide sequence of the target nucleic acid.

2. (Previously Presented) The method of claim 1, wherein each Raman-active oligonucleotide probe intrinsically generates a detectable Raman signal.

3. (Previously Presented) The method of claim 2, wherein the at least one Raman-active oligonucleotide is composed of less than 5 purine residues.

4. (Previously Presented) The method of claim 3, wherein the at least one Raman-active oligonucleotide comprises no purine residues.

5. (Previously Presented) The method of claim 1, wherein at least one of the Raman-active oligonucleotides comprises a composite of organic-inorganic nanoparticles.

6. (Original) The method of claim 1, wherein the determined nucleotide sequence is a nucleotide occurrence at a target nucleotide position.

7. (Original) The method of claim 6, wherein the target position is a single nucleotide polymorphism position.

8. (Original) The method of claim 1, wherein the determined nucleotide sequence is a series of nucleotide occurrences at adjacent positions of a target segment.

9. (Original) The method of claim 8, wherein the target segment is less than or equal to the combined length of the capture oligonucleotide probe and the Raman-active oligonucleotide probe.

10. (Original) The method of claim 8, wherein the target segment is less than or equal to the length of the Raman-active oligonucleotide probe.

11. (Original) The method of claim 8, wherein the nucleotide sequence of the entire target nucleic acid is determined by aligning detected target sequences.

12. (Original) The method of claim 1, further comprising ligating the capture oligonucleotide probes to Raman-active oligonucleotide probes that bind to an adjacent segment of the target nucleic acid.

13. (Original) The method of claim 1, wherein the target nucleic acid is isolated from a biological source and contacted with the population of capture oligonucleotide probes, without amplification.

14. (Original) The method of claim 13, wherein 1000 or less molecules of the Raman-active oligonucleotide probe are detected.

15. (Original) The method of claim 1, wherein the substrate is a biochip.

16. (Previously Presented) The method of claim 1, wherein the Raman-active oligonucleotide probe is detected using surface enhanced Raman spectroscopy (SERS).

17. (Original) The method of claim 1, wherein a first population of Raman-active oligonucleotide probes are contacted with the probe-target duplex nucleic acids at a first spot of a series of spots, and a second population of Raman-active oligonucleotide probes are contacted with the probe-target duplex nucleic acids at a second spot of the series of spots, wherein the first population of Raman-active oligonucleotide probes and the second population of Raman-active oligonucleotide probes comprise at least one different oligonucleotide probe.

18-21. (Cancelled)

22. (Currently amended) A method to determine a nucleotide occurrence at a target nucleotide position of a template nucleic acid, comprising:

a) providing a labeled oligonucleotide probe that binds to the target polynucleotide, wherein the labeled oligonucleotide probe comprises a first label and a second label, the first label affecting the Raman spectra or fluorescent signal generated by the second label based on the orientation of the first label to the second label;

b) contacting the labeled oligonucleotide probe with the target polynucleotide to form a probe-target complex;

c) ~~applying pre-made aggregates of metallic~~ aggregating metal colloids or nanoparticles ~~to~~ with the probe-target complex in the presence of a mono-valent salt, wherein the metal colloids are pre-made;

d) applying an alternating current (AC) to the probe-target complex prior to detection, wherein the applied AC enhances the difference in the affect of the first ~~probe~~label on the second

~~probe~~label fluorescent signal or Raman spectra; and

e) detecting the fluorescent signal or Raman spectra generated by the second label, wherein the nucleotide occurrence at the target nucleotide position affects the orientation of the first label to the second label, thereby affecting the fluorescent signal or Raman spectra generated by the second label and allowing determination of the nucleotide occurrence at the target nucleotide position.

23. (Original) The method of claim 22, wherein a fluorescent signal is detected.

24. (Original) The method of claim 23, wherein the first label and the second label are a FRET pair.

25. (Original) The method of claim 24, wherein one label is TAMRA and another label is ROX.

26. (Original) The method of claim 22, wherein a Raman spectra is detected.

27. (Original) The method of claim 26, further comprising comparing the detected Raman spectra to a database of known spectra to identify the nucleotide occurrence at the target nucleotide position of the target polynucleotide.

28. (Original) The method of claim 22, wherein the first label and the second label are located about 3-6 nm apart on the labeled probe sequence.

29. (Original) The method of claim 22, wherein a series of nucleotide occurrences for one or more target nucleotides are determined using a population of labeled probes.

30. (Original) The method of claim 29, wherein probe-target complexes are individually passed through an optical detector to read the fluorescent signal or Raman spectra generated by the probe-target complexes.

31. (Original) The method of claim 29, wherein individual probe-target complexes are individually passed through an optical detector using a microelectromechanical system having a channel that is sufficiently narrow to allow only one probe-target complex to pass.

32. (Previously Presented) The method of claim 22, wherein an alternating current (AC) is applied at 10 mV to 100 mV, with an AC frequency of 1 Hz to 1 MHz.

33. (Currently amended) A method for detecting a nucleic acid, comprising:

a) irradiating the nucleic acid with light, wherein the nucleic acid is covalently attached to a positively charged Raman signal enhancer, wherein the positively charged Raman signal enhancer comprises a primary amine Raman signal enhancer having an alkyl chain of 1 to 25 carbon atoms and, the positively charged Raman signal enhancer maintains its positive charge after binding with the probe-target complex;

and

b) detecting a Raman signal generated by the irradiated nucleic acid.

34. (Previously Presented) The method of claim 33, wherein the nucleic acid comprises less than 5 purine residues positively charged enhancer is an amine group.

35. (Cancelled)

36. (Original) The method of claim 33, wherein the nucleic acid consists of pyrimidine residues.

37. (Original) The method of claim 1, wherein at least a portion of the single-stranded overhangs is a constituent of the target nucleic acid.

38. (Currently amended) The method of claim 1, wherein at least one of the Raman-active oligonucleotide probes further comprises a Raman tag attached to ~~the backbone of the~~ at least one of the Raman-active oligonucleotide probes.

39. (Previously Presented) The method of claim 22, wherein the labeled oligonucleotide probe comprises a tag attached to the backbone of the labeled oligonucleotide probe.

40. (Previously Presented) The method of claim 33, wherein the nucleic acid comprises a Raman tag attached to the backbone of the nucleic acid.

41. (Previously Presented) The method of claim 1, further comprising aggregating pre-made metallic colloid or aggregate of nanoparticles with said at least one of the Raman active oligonucleotide probes comprising the positively charged Raman signal enhancer.

42. (Previously Presented) The method of claim 33, further comprising aggregating pre-made metallic colloid or aggregate of nanoparticles with said nucleic acid covalently attached to a positively charged Raman signal enhancer.

43. (Previously Presented) The method of claim 1, wherein the positively charged Raman signal enhancer comprises a primary amine Raman signal enhancer having an alkyl chain of from 1 to 25 carbon atoms.

44. (Previously Presented) The method of claim 41, wherein said aggregating is in the presence of a mono-valent salt.

45. (New) The method of claim 1, wherein the positive charge on the positively charged Raman signal enhancer is carried by a heteroatom, the hetero atom excluding N, O, and S.